investigate a wide protein concentration and pH range of 2 mg/mL $\leq$ [Protein] $\leq$ 500 mg/mL and 3.0 $\leq$ pH $\leq$ 11 and find clear evidence for pH and concentration dependencies of conformation from our SANS data. The data are successfully modeled using the random-phase approximation (RPA), where we use a phenomenological model for the form factor that is able to capture contributions from both monomers and clusters in solution. Owing to the separability of the form factor into contributions from monomers and clusters, we are able to obtain structure factors that reflect monomer-monomer, monomer-cluster, and cluster-cluster correlations in solution, which allows us to gain realistic insights into packing and intermolecular interactions at high concentrations. We use these data as inputs into a modification of the model developed by Minton for protein mixtures, which can accurately capture the contributions of monomer and clustered species to model the concentration and pH dependent viscosity of BSA and the IgG1 solution.

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All-Atom Molecular Dynamic Simulations of Pulmonary Surfactant Protein Sp-B Interacting with Lipid Bilayers

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Pulmonary lung surfactant protein B (SP-B) is a hydrophobic protein with 79 residues, from the saposin superfamily. The saposin superfamily proteins have a conserved pattern of 3 intra-chain disulfide bonds. SP-B associates with phospholipids at the air/water interface of the lungs and plays an essential role in respiration. Its mechanism appears to relate to SP-B's ability to modify the structures of phospholipid bilayers and monolayers. An experimental 3D structure of SP-B has not yet been determined. It is possible to produce homology models of SP-B based on other saposin superfamily proteins such as NK-Lysin, Saposin B, and Saposin C. However, the homology is relatively low and it is not known exactly which segments of SP-B are helical. More importantly, it is not clear if SP-B forms a closed structure, as in NK-lysin, or a more open structure, as in Saposin C. Whether SP-B is open or closed vastly modifies the hydrophobic surface that is exposed and the consequent mechanisms for interacting with the phospholipids. In this work, we start with different homology model structures for SP-B and different initial topologies for SP-B interacting with POPC lipid bilayers. Molecular dynamics simulations are carried out using GROMACS with the all-atom force field OPLS-AA.

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Membrane Properties Affect Opening Behaviors of the Bacterial Mechanosensitive Channel MscL: Molecular Dynamics Study

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Mechanosensitive channel MscL is constituted of homopentamer of a subunit with two transmembrane inner (TM1) and outer (TM2) helices and its 3D structure of the closed state has been resolved. TM1s line an ion permeable pore and cross each other near cytoplasmic side, forming the most constricted part of the pore called gate. TM2s face lipids and some amino acids in TM2 act as a tension sensor. MscL is activated by sensing membrane tension and the major issue of MscL is to understand the gating mechanism driven by membrane tension. Previous studies propose that MscL embedded in thin membrane can activate with a lower threshold than that embedded in thick membrane. However, it remains unclear how MscL activation (opening of the gate) depends on membrane thickness in detail. In this study, we performed molecular dynamics (MD) simulations of MscL embedded in four types of lipid bilayer with different membrane thickness (DLPC, DMPC, DPPC and DSPC) to get insight into the dependency at an atomic level. As a result, it was shown also in our results that MscL in a thin lipid bilayer DLPC opened more widely than that embedded in a thick lipid bilayer DSPC. Furthermore, it was found that the thinner membrane tended to make the transmembrane helices of MscL tilt more largely. In order to check MscL-lipid interactions, we calculated the interaction energy between MscL and lipids and found that the interaction energy between Phe93 and lipids, located at the cytoplasmic side, was smaller as the membrane was thinner. This seems to be due to a hydrophobic mismatch between MscL and lipids, which affect the tilting of transmembrane helices followed by expanding of the gate during opening.

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Molecular Dynamics Analysis on the Role of the N-Terminal Domain in Mechano-Gating of E-Coli Mechanosensitive Channel MscL

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The bacterial mechanosensitive channel MscL is constituted of homopentamer of a subunit with two transmembrane inner and outer (TM1, TM2) α-helices, and its 3D structure of the closed state has been resolved. The major issue of MscL is to understand the gating mechanism driven by tension in the membrane. To address this question, molecular dynamics (MD) studies have been performed, however, as they do not include MscL-lipid interactions, it remains unclear which amino acids sense membrane tension and how the sensed force induces channel opening. Thus we performed MD simulations for the opening of MscL embedded in the lipid bilayer. Among amino acids in TM2 facing the bilayer, Phe78 showed exceptionally strong interaction with lipids. Upon membrane stretch, Phe78 was dragged by lipids, leading to an opening of MscL. Thus Phe78 was concluded to be the major tension sensor. Neighboring TM1s cross and interact with each other near the cytoplasmic side through hydrophobic interaction between Leu19-Val23 in one TM1 and Gly22 in the neighboring TM1, forming the most constricted hydrophobic part of the pore called gate. Upon membrane stretch, the helices are dragged by lipids at Phe78 and tilted, accompanied by the outward sliding of the crossings, leading to expanding of the gate. In this study, we newly modeled the Eco-MscL with the N-terminal (S1) helices running parallel to the cytoplasmic membrane instead of forming the tight bundle proposed previously and determined the role of the S1 helices in channel opening. As a result, RMSD of the newly modeled MscL was smaller and the channel opened faster than the previous one, suggesting that the newly modeled S1 helices play a role of stabilizing the channel in closed and accelerating the opening.

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Continuum Electrostatic Approach for Evaluating Membrane Protein Positions in Membrane

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The spatial orientation of membrane proteins within the lipid environment has been evaluated based on Poisson-Boltzmann (PB) solvent continuum approach. The strategy involves in the calculation of the electrostatic free energy of the protein solvation at various orientations in the lipid bilayer. The solvation free energy is obtained by computing the difference in electrostatic energies of the protein immerged in water and lipid environments treated as implicit solvent models. In the evaluation carried out for a number of ion channel membrane proteins and soluble proteins, the results showed a distinguish pattern of the solvation energy landscapes between transmembrane proteins and soluble proteins. The study also showed that the electrostatic contribution for transferring proteins from the high-dielectric aqueous phase to a lower-dielectric membrane environment is always unfavourable. Furthermore, detailed energy analysis of five types of membrane proteins provides two distinct patterns of the solvation energy that are useful for discriminating between transmembrane and non-transmembrane proteins. Finally, the evaluation of the position of membrane proteins available from Orientations of Proteins in Membranes (OPM) database has been achieved for a total of 1060 proteins. In the case of transmembrane proteins, most of the tested proteins are in good agreement with those of the OPM database. The results for non-transmembrane α-helical and peripheral/monotopic proteins appear to contradict that there is no apparent minimum. It is expected that the present approach is of great assistance for constructing protein-lipid structure systems suitable for experimental and computational studies.

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Protein-Protein and Protein-Membrane Interactions Regarding the Erbb2/Trastuzumab-Fab Complexes. A Coarse-Grained Molecular Dynamics Description

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ErbB2 is a member of epidermal growth factor receptor (EGFR) family and is overexpressed in many cancers. Specifically, Trastuzumab, which is a monoclonal antibody, is used against ErbB2, but its action mechanism is still unknown. ErbB2 can exist as both monomers and Homodimers, suggesting that Trastuzumab mechanims may be subtle. On the other hand, the membrane plays a role in the action mechanism of Trastuzumab but generates difficulties for structural studies. Coarse-Grained Molecular Dynamics has been used to study the influence of the Trastuzumab on the protein-protein and protein-membrane interactions of the full ErbB2 receptor. Our simulations start from conformations which both extracelullar and intracelullar domains are extended. The results show in both monomers and homodimers systems a folded conformation on the membrane: several experimental results, mainly obtained on ErbB1 support them. The protein-protein interaction on transmembrane and juxtamembrane domains are disrupted on the dimer and disordered on the monomer by the Trastuzumab effect, therefore, the dimerization-driven activation are unfavourable. We present a detailed description